Complete Summary

GUIDELINE TITLE

Guidelines for the diagnosis and therapy of adult myelodysplastic syndromes.

BIBLIOGRAPHIC SOURCE(S)

Bowen D, Culligan D, Jowitt S, Kelsey S, Mufti G, Oscier D, Parker J, UK MDS Guidelines Group. Guidelines for the diagnosis and therapy of adult myelodysplastic syndromes. Br J Haematol 2003 Jan;120(2):187-200. [89 references] PubMed

GUIDELINE STATUS

This is the current release of the guideline.

** REGULATORY ALERT **

FDA WARNING/REGULATORY ALERT

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory information has been released.

- July 31, 2008, Erythropoiesis Stimulating Agents (ESAs): Amgen and the U.S. Food and Drug Administration (FDA) informed healthcare professionals of modifications to certain sections of the Boxed Warnings, Indications and Usage, and Dosage and Administration sections of prescribing information for Erythropoiesis Stimulating Agents (ESAs). The changes clarify the FDA-approved conditions for use of ESAs in patients with cancer and revise directions for dosing to state the hemoglobin level at which treatment with an ESA should be initiated.
- November 8, 2007 and January 3, 2008 Update, Erythropoiesis Stimulating Agents (ESAs): The U.S. Food and Drug Administration (FDA) notified healthcare professionals of revised boxed warnings and other safety-related product labeling changes for erythropoiesis-stimulating agents (ESAs) stating serious adverse events, such as tumor growth and shortened survival in patients with advanced cancer and chronic kidney failure.

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Adult myelodysplastic syndromes (MDS)

GUIDELINE CATEGORY

Diagnosis
Management
Treatment

CLINICAL SPECIALTY

Hematology
Oncology

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

To critically review individual therapeutic modalities designed to improve the clinical problems specific to an individual patient with myelodysplastic syndromes (MDS), and to provide recommendations for management strategies driven by the patient's International Prognostic Scoring System (IPSS) score and the overall clinical picture

TARGET POPULATION

Adults with myelodysplastic syndromes (MDS)

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Evaluation

1. Exclusion of reactive causes of dysplasia
2. Patient and family history
3. Physical examination
4. Full blood count
5. Blood film
6. Assay of serum ferritin, Vitamin B12 and folate levels

7. Bone marrow aspirate
8. Bone marrow trephine biopsy
9. Bone marrow cytogenetic analysis

Management/Treatment

1. Red cell transfusion
2. Iron chelation therapy
    - Desferrioxamine (with audiometry and ophthalmology review and vitamin C)
3. Erythropoietin (EPO) +/− granulocyte colony-stimulating factor (G-CSF)
4. Immunosuppression therapy
    - Anti-lymphocyte globulin (ALG)
5. Thrombocytopenia therapy
    - Antifibrinolytic agents
    - Danazol
    - Platelet transfusions
6. Infection management
    - Prophylactic (G-CSF)
    - Therapeutic (intravenous antibiotics)
7. Chronic myelomonocytic leukaemia therapy
    - Hydroxyurea
8. Intensive chemotherapy/stem cell transplantation
9. Chemotherapy alone
10. Supportive care/investigational therapy

MAJOR OUTCOMES CONSIDERED

- Response to therapy
- Adverse effects of therapy
- Quality of life
- Survival

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Medline/Pubmed was systematically searched from 1982. The Cochrane database was searched but contained no references to myelodysplastic syndromes (MDS). Meeting abstracts were not included in the systematic search strategy.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

Ia Evidence obtained from meta-analysis of randomized controlled trials.

1b Evidence obtained from at least one randomized controlled trial.

IIa Evidence obtained from at least one well-designed controlled study without randomization.

IIb Evidence obtained from at least one other type of well-designed quasi-experimental study

III Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case studies.

IV Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review with Evidence Tables

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

The guideline group was selected to include UK-based medical experts in the clinical management of myelodysplastic syndromes (MDS) and to include a representative from a District General Hospital. The drafting group met on six occasions. Each group member was allocated responsibility for preparation of a selected component of the first draft.

The Chairman synthesized the draft components, which were revised by consensus through meetings 3–6. No recommendations are included for which full consensus was not achieved.

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Grades of Recommendations

Grade A, evidence level Ia, Ib

Required - at least one randomised controlled trial of good quality and consistency addressing specific recommendation.

Grade B, evidence level IIa, IIb, III

Required - availability of well-conducted studies but no randomised controlled trials on the topic of recommendation.

Grade C, evidence level IV

Required - evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities.

Indicates absence of directly applicable clinical studies of good quality.

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

The draft guideline was reviewed by the Sounding Board and by the Committee of the British Committee for Standards in Haematology, and comments incorporated where appropriate. Following further helpful peer-review by the British Journal of Haematology, a final revision was presented.

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The levels of evidence **(I–IV)** and strength of recommendations **(A–C)** are defined at the end of the "Major Recommendations" field.

Diagnosis

The diagnosis and classification of myelodysplastic syndromes (MDS) remain dependent on the morphological examination of blood and bone marrow cells. Diagnostic criteria should ideally distinguish MDS from reactive conditions causing dysplastic haematopoiesis and from other clonal myeloid disorders. The minimum clinical assessment and laboratory investigation required for the definitive diagnosis of cases of suspected MDS is shown in the table below.

Evaluation of suspected MDS

History
Prior exposure to chemotherapy/radiation
Family history of MDS/acute myeloid leukaemia (AML)
Recurrent infections or bleeding/bruising
Examination
Pallor/infection/bruising
Splenomegaly
Full blood count
Macrocytosis, cytopenia(s), neutrophilia, monocytosis, thrombocytosis
Blood film
Assay of serum ferritin, vitamin B12 and folate levels
Bone marrow aspirate
Bone marrow trephine biopsy
Bone marrow cytogenetic analysis
Exclusion of reactive causes of dysplasia
Megaloblastic anaemia
Human immunodeficiency virus infection
Alcoholism
Recent cytotoxic therapy
Severe intercurrent illness

Management of Myelodysplastic Syndromes

Where possible, management decisions be based upon the patient's International Prognostic Scoring System (IPSS) score. It is important that the IPSS score is calculated during a stable clinical state, and not, for example, during a florid infective initial presentation. Management decisions should be taken with the informed involvement of the patient and, to aid this, information booklets are

available from the Leukaemia Research Fund and the Myelodysplastic Syndromes Foundation.

Supportive Care: Principles

For patients with good prognosis MDS, it is often feasible to undertake a period of observation without needing to introduce specific therapy. Where possible, this 'wait and watch' approach to management may also be useful for patients with more advanced MDS, allowing one to appraise the stability of the disease process and to assess the need to introduce treatment.

Management of Anaemia

Red cell transfusion and iron chelation therapy

Recommendations for iron chelation treatment in myelodysplasia are based on limited data (**evidence grade B, level III**). Iron chelation should be considered once a patient has received 5 g iron (approximately 25 units of red cells) but only in patients for whom long-term transfusion therapy is likely, such as those with pure sideroblastic anaemia or the $5q^-$ syndrome. Desferrioxamine 20–40 mg/kg should be administered by 12 hour subcutaneous infusion 5–7 days per week. Audiometry and ophthalmology review are essential prior to commencement of desferrioxamine. The target ferritin concentration should be < 1000 microg/L; if the ferritin concentration falls below < 2000 microg/L, the dose of desferrioxamine should be reduced and should not exceed 25 mg/kg. Vitamin C 100–200 mg daily should be commenced after 1 month of desferrioxamine therapy. Vitamin C should be taken when the infusion is set up. Repeat audiometry and ophthalmology review should be performed at least annually. The use of twice daily subcutaneous bolus injections of desferrioxamine may be considered where infusions are not tolerated, but the common practice of adding a single dose of desferrioxamine at each transfusion episode has no basis and should be discouraged.

Erythropoietin (EPO) +/– granulocyte colony-stimulating factor (G-CSF)

Many studies have clearly demonstrated that EPO ± G-CSF can increase haemoglobin concentration and reduce/eliminate red cell transfusion in selected MDS patients, and a summary outline of these is provided in Tables IVA and B of the original guideline document. These studies were small cohort studies (< 120 patients in each) and only one (small) placebo-controlled randomized study (of EPO therapy alone) has been reported. Given the small size of this placebo-controlled trial of EPO therapy alone (87 patients), the grade of recommendation for EPO therapy alone should be considered as **grade A/B** (**level Ib/IIa**). The evidence for efficacy of the combination of EPO + G-CSF therapy is **grade B** (**level IIa/IIb**).

Overall there is sufficient evidence for the efficacy of EPO ± G-CSF therapy in appropriately selected patients. It is recommended that those patients with refractory anaemia (RA) and RA with excess blasts (RAEB, not eligible for chemotherapy/stem cell transplantation [SCT]) who are symptomatic of anaemia, with no/low transfusion requirement (< 2 units/month) and a basal EPO level of less than 200 U/L (measured at the haemoglobin nadir in transfusion-dependent

patients) be considered for a trial of EPO alone at a dose of 10,000 units daily for 6 weeks. For non-responders, consideration should be given to either the addition of daily G-CSF, doubling the dose of EPO, or both for a further 6 weeks. The dose of G-CSF should be escalated weekly from 75 microg, to 150 microg to 300 microg (multiple sampling from single vials kept at 4°C) to maintain the white blood cell count between 6 and 10×10^9/L.

In responding patients, once the maximum response has been reached, the G-CSF can be reduced to thrice weekly and the EPO to 5 days then 4 d to 3 days per week at 4 weekly intervals to the lowest dose that retains response.

For patients with RA with ringed sideroblasts (RARS), symptomatic anaemia, basal EPO levels of < 500 U/L and a transfusion requirement of less than 2 units per month, it is recommended that combined therapy with EPO and G-CSF is used from the outset. Dosing recommendations are as for RA/RAEB with consideration given to dose escalation of EPO at 6 weeks in non-responders for a further 6 weeks.

Immunosuppression

The data support a recommendation for a trial of immunosuppressive therapy with anti-lymphocyte globulin (ALG) at least for patients with hypoplastic MDS (**evidence grade B, level IIb**).

Management of thrombocytopenia

The role of platelet transfusions in MDS patients should be based on the Royal College of Physicians of Edinburgh Consensus Conference Statement. Antifibrinolytic agents (**grade C, level IV**) and Danazol (**grade B, level IIb**) are occasionally useful but cannot be routinely recommended.

Management of infection

Prophylactic

There are no published data to support the routine use of antibacterial or antifungal prophylaxis in neutropenic MDS patients. Consideration may be given to the use of prophylactic low-dose G-CSF therapy in severely neutropenic patients to maintain the neutrophil count > 1×10^9/L (**grade B, level IIb**)

Therapeutic

Neutropenic sepsis in MDS patients should be treated with intravenous antibiotics as for other patients with neutropenia (e.g. post chemotherapy).

Chronic myelomonocytic leukaemia (CMML)

CMML often has a myeloproliferative component, and cytoreductive chemotherapy is frequently indicated. Hydroxyurea is considered the standard treatment for CMML, in preference to oral etoposide (**evidence grade A, level Ib**)

Intensive chemotherapy/stem cell transplantation

It is recommended that clinicians discuss all patients eligible for stem cell transplantation with their local transplant unit.

IPSS Low

Neither intensive chemotherapy nor stem cell transplantation can currently be recommended for this group whose median survival without treatment is 4·8 (> 60 years)-11·8 years (< 60 years).

IPSS INT-1

All patients < 65 years should be assessed for fitness/eligibility for allogeneic SCT as soon as possible after diagnosis, as SCT outcome is improved if performed early. If eligible and a sibling donor is available, it is recommended that patients < 50 years are offered ablative allogeneic SCT (**evidence grade B, level IIb**) and patients > 50 < 65 years are considered for non-ablative allogeneic SCT, within clinical trials where available (**evidence grade C, level IV**). Patients with no sibling donor, but with an unrelated donor should also be considered for ablative unrelated-donor SCT (< 40 years, **evidence grade B, level III**) or non-ablative unrelated-donor SCT within clinical trials (> 40 years, **evidence grade C, level IV**), though the transplant related mortality (TRM) from these procedures remains high. Intensive cytoreductive chemotherapy prior to SCT is not recommended for this group (**evidence grade B, level IIb**).

Patients > 65 years or < 65 years and not suitable for SCT should be offered supportive care and/or considered for growth factor therapy (e.g., EPO). Recommendations for the management of IPSS INT-1 MDS patients $\leq$ 65 years are outlined in Figure 2 of the original guideline document.

IPSS INT-2/High

Chemotherapy plus SCT

All patients < 65 years should again be considered as to fitness/eligibility for stem cell transplantation early after diagnosis. In this group of high-risk patients, stem cell transplantation should only be considered for those responding to remission induction chemotherapy (complete/good partial response) as the outcome for non-responding patients is very poor (**evidence grade B, level IIb**). For patients < 65 years, eligible for SCT and responding to chemotherapy, recommendations for SCT consolidation are outlined in Figure 3 of the original guideline document.

Chemotherapy alone

Both patients > 65 years and those < 65 years who are ineligible for stem cell transplantation should be considered for intensive chemotherapy alone.

Cohort studies suggest that of all high-risk MDS patients ($\geq$ INT-2), those with RAEB in transformation (20–30% marrow blasts) and lacking an independent adverse risk factor [karyotype, age, performance status, length of antecedent

haematological disorder] respond best to intensive 'AML-type' chemotherapy (**evidence grade B, level IIb**). Thus, intensive chemotherapy alone is recommended for consideration in these patients.

In all other high-risk MDS patients (namely those for whom intensive chemotherapy alone is not recommended), intensive remission-induction chemotherapy (two courses) should be offered only if stem cell transplantation is proposed as consolidation (Figure 3 of the original guideline document).

Supportive Care/Investigational Therapy

If patients do not fall into any category for which chemotherapy ± SCT is recommended they should be offered supportive care or investigational therapies within clinical research protocols.

Definitions:

Levels of Evidence

Ia Evidence obtained from meta-analysis of randomized controlled trials.

1b Evidence obtained from at least one randomized controlled trial.

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IIb Evidence obtained from at least one other type of well-designed quasi-experimental study

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Grades of Recommendations

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Grade C, evidence level IV

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Indicates absence of directly applicable clinical studies of good quality.

CLINICAL ALGORITHM(S)

Three clinical algorithms are provided in the original guideline document:

- Guidelines for the management of symptomatic anaemia in myelodysplastic syndromes (MDS) patients
- Guidelines for the management of International Prognostic Scoring System (IPSS) INT-1 MDS patients aged $\leq$ 65 years
- Guidelines for stem cell transplantation (SCT) in the management of IPSS INT-2/high MDS patients aged $\leq$ 65 years

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for most of the recommendations (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Accurate diagnosis and appropriate management of myelodysplastic syndromes (MDS), including control of disease, prevention of complications, improved quality of life, and prolonged survival

POTENTIAL HARMS

- Side effects of treatment
- Transplant related mortality

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- It is important to stress that most recommendations are made on the basis of a very limited evidence base for the efficacy of interventional and non-interventional therapy in myelodysplastic syndromes (MDS). Most papers reporting interventional therapy describe relatively small cohorts of patients and only one (small) placebo-controlled trial is available. Criteria for defining therapeutic response are also highly variable between studies.
- Supportive care remains the most important aspect of management for patients with good prognosis MDS and those with poor prognosis disease whose age or performance status precludes them from receiving more

intensive forms of therapy. However, grade A and grade B evidence for the effectiveness of supportive care in patients with myelodysplasia is absent and is unlikely to ever be obtainable.
- Whilst the advice and information contained in this guideline are believed to be true and accurate at the time of going to press, neither the authors nor the publisher can accept any legal responsibility or liability for any errors or omissions that may be made.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Bowen D, Culligan D, Jowitt S, Kelsey S, Mufti G, Oscier D, Parker J, UK MDS Guidelines Group. Guidelines for the diagnosis and therapy of adult myelodysplastic syndromes. Br J Haematol 2003 Jan;120(2):187-200. [89 references] PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2003 Jan

GUIDELINE DEVELOPER(S)

British Committee for Standards in Haematology - Professional Association

SOURCE(S) OF FUNDING

British Committee for Standards in Haematology

GUIDELINE COMMITTEE

UK MDS Guidelines Group

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

Group Members: David Bowen, Molecular and Cellular Pathology, Ninewells Hospital, Dundee; Dominic Culligan, Aberdeen Royal Infirmary, Aberdeen; Simon Jowitt, Stepping Hill Hospital, Stockport; Stephen Kelsey*, Department of Oncology, St. Bartholomews and Royal London MDS, London; Ghulam Mufti, Department of Haematological Medicine, King's College of Medicine and Dentistry, London; David Oscier, Royal Bournemouth Hospital, Bournemouth, UK; Jane Parker, Department of Haematological Medicine, King's College of Medicine and Dentistry, London

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Meeting expenses were covered by support from Janssen-Cilag. Dr Stephen Kelsey became an employee of Pharmacia Upjohn during the guideline preparation process. Dr Culligan and Professor Mufti are members of the ROCHE Steering Group for the treatment of cancer-related anaemia.

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available from the British Committee for Standards in Haematology Web site.

Print copies: Available from Dr David Bowen, Consultant Haematologist, Department of Hematology, Brotherton Wing D Floor, Leeds General Infirmary, Great George Street, Leeds, LS1 3EX; Telephone: 44 113 392 5153; Fax: 44 113 392 6349; E-mail: david.bowen@leedsth.nhs.uk

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

None available

NGC STATUS

This NGC summary was completed by ECRI on September 28, 2006. The information was verified by the guideline developer on October 25, 2006. This

summary was updated by ECRI on January 29, 2007, following the U.S. Food and Drug Administration advisory on erythropoiesis stimulating agents. This summary was updated by ECRI Institute on July 9, 2007, following the FDA advisory on erythropoiesis stimulating agents. This summary was updated by ECRI Institute on March 21, 2008 following the FDA advisory on Erythropoiesis Stimulating Agents. This summary was updated by ECRI Institute on August 15, 2008 following the U.S. Food and Drug Administration advisory on Erythropoiesis Stimulating Agents (ESAs).

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